Section Editor: **Sorin J. Brull**

The Association Between Preoperative Anemia and 30-Day Mortality and Morbidity in Noncardiac Surgical Patients

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BACKGROUND: Anemia has been associated with increased postoperative morbidity and mortality. We used the American College of Surgeons National Surgical Quality Improvement Program database to retrospectively assess the relationship between preoperative anemia and 30-day postoperative mortality and morbidity in noncardiac surgical patients, careful to distinguish confounding variables from mediator variables.
METHODS: Each patient with preoperative anemia was matched to one without anemia using propensity matching on potentially confounding baseline variables. Logistic regression was used to evaluate the relationship between preoperative anemia and 30-day postoperative mortality and morbidity. The primary hypothesis was evaluated after adjusting for covariables showing residual imbalance after matching.
RESULTS: Within the database, 574,860 of 971,455 surgical cases met our inclusion criteria, and among those 145,218 (25.3%) were anemic at baseline. The unadjusted odds ratio (95% confidence interval) for 30-day mortality comparing anemic patients with nonanemic patients was 4.69 (4.01–5.49). Among the propensity-matched group of 238,596 patients, the total effect (i.e., not adjusting for mediator variables) of preoperative anemia was estimated as an odds ratio of 1.59 (1.42–1.78). After adjusting for suspected mediator variables, preoperative anemia was only weakly associated with an odds ratio of 1.24 (1.10–1.40) for 30-day mortality.
CONCLUSION: Preoperative anemia appears to be associated with baseline diseases that markedly increase mortality. Anemia per se is a rather weak independent predictor of postoperative mortality. Our analysis also illustrates how analyzing large variable-rich registries challenges investigators to discriminate between confounding variables and mediator variables, i.e., factors that might be considered as "causal pathways" for the effect of the exposure or intervention on outcome. (Anesth Analg 2013;117:909–15)

Anemia is an important problem during the perioperative period. It is independently associated with myocardial infarction,[1] decreased glomerular filtration rate,[2] and congestive heart failure.[3] Mortality is increased in patients with acute coronary syndrome,[1,4] heart failure,[5] chronic angina,[6] and after noncardiac[3,7–11] and cardiac surgeries.[12,13] Furthermore, preoperative anemia puts patients at a higher risk for receiving blood transfusions. As might be expected, anemic patients receive more transfusions than nonanemic patients.[14–17] Although transfusions may treat anemia, they are associated with numerous serious morbidities such as renal failure, prolonged ventilator support, increased perioperative infection risk, cardiovascular complications,[18] and mortality.[18–24]

Several retrospective studies of clinical and administrative databases suggest that preoperative anemia significantly worsens postoperative outcomes in general surgical populations as well as in specific high-risk subpopulations.[7,11,25–27]

Generalizability of the aforementioned, mostly, retrospective studies is possibly limited by single-center effects,[7] inclusion of specific patient populations,[11,27] or specific statistical approaches[10] resulting in large variations in effect sizes. The reason for this variation might be that large electronic registries used for these studies contain a multitude of baseline, intraoperative, and postoperative variables, and that careful consideration of potential confounding variables and associated selection bias is essential. Most previous studies do not clearly distinguish between confounding factors (i.e., variables potentially affecting both anemia and outcome) and mediating variables (i.e., variables that might be caused by anemia and also mediate the effect of anemia on outcome). A "kitchen sink" approach of adjusting for all available variables may lead to overadjustment and therefore bias (and likely underestimation) of the true anemia effect.

We therefore used the American College of Surgeons National Surgical Quality Improvement Program (NSQIP)

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Accepted for publication January 4, 2013

This work was supported by departmental funding only.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0b013e31828b347d

Table 1. Diagram of Study Flow

971,455 surgical cases in National Surgical Quality Improvement Program
3513 patients with RBC transfusion >4 units in 72 h before surgery removed
5051 patients with cardiac surgery
53,213 patients with bleeding disorders
108,057 patients with emergency cases
79,209 patients with prior surgery in 30 d preceding day of surgery
23,511 patients with RBC transfusion >4 units in 72 h before surgery removed
698,901 patients included in the study
25 patients with missing gender
114,816 patients with missing preoperative hematocrit
9200 patients with missing potential confounders
574,860 patients available for analysis

RBC = red blood cell.

data to determine whether preoperative anemia (defined as a hematocrit <36% for female patients and <39% for male patients) is related to 30-day mortality or other 30-day morbid outcomes. Specifically, we used chronic exposure such as preoperative anemia and its relation to postoperative outcomes to demonstrate how distinguishing predefined clinically chosen confounding variables from potential mediating variables is essential to proper estimation and interpretation of the relationship of interest.

METHODS

NSQIP is an externally validated, prospective quality improvement initiative, for which participating institutions employ full-time clinical nurse reviewers to ensure the integrity of patient, surgical, and 30-day outcomes data. Data pertaining to patients undergoing certain low-morbidity, high-volume procedures are limited to avoid overwhelming the registry. Patients included in the NSQIP registry are enrolled in a site-specific 8-day cycle to avoid systematic bias introduced by weekly patterns in case loads.[28] We obtained data on NSQIP-participating patients, treated at 1 of >230 centers between 2005 and 2009, from the American College of Surgeons.

Patients studied included all elective noncardiac cases. We excluded patients with transfusion of >4 red blood cell (RBC) units in the 72 hours before surgery, prior surgery within 30 days, bleeding disorders (e.g., vitamin K deficiency, hemophilia, thrombocytopenia, or chronic anticoagulation therapy that had not been discontinued before surgery), and septic disease (defined as systemic inflammatory response syndrome, sepsis, or septic shock). Patients with unavailable gender or preoperative hematocrit were excluded as well (Table 1).

We studied as our primary analysis the respective relationships between anemia (defined as hematocrit <36% for female patients and <39% for male patients, based on the World Health Organization's gender-based definition[a]) and 30-day postoperative outcomes: mortality, cardiac complications (including acute myocardial infarction and cardiac arrest requiring resuscitation), central nervous system complications (including stroke, coma longer than 24 hours postoperatively, and peripheral nerve injury), respiratory complications (including pneumonia, failure to wean from ventilation at 48 hours postoperatively, and unplanned intubation), systemic complications (including systemic inflammatory response syndrome, sepsis, and septic shock), thrombotic complications (including pulmonary embolism, deep venous thrombosis, and thrombophlebitis), urinary complications (including urinary tract infections, progressive renal insufficiency, and acute renal failure), wound infection (including superficial and deep wound infections, organ/space infections, and wound disruptions), and return to the operating room.

We distinguished confounders (i.e., variables potentially affecting both anemia and outcome) from 6 mediating variables (i.e., variables that might be caused by anemia and also mediate the effect of anemia on outcome). Specifically, the comparison of anemic patients to healthy patients for a given outcome can vary substantially depending on whether only potential confounding variables have been included in the model or whether potential mediator variables have also been included. We differentiated certain variables as potential confounders and others as potential mediators based on clinical considerations. This was done a priori in a formal process by 3 different anesthesiologists independently; any differences in opinion were arbitrated by a majority vote afterward. This is admittedly subjective to a certain degree, but we seek to emphasize the fact that any analysis of chronic exposures is subject to these clinical opinions. Figure 1 illustrates an example of confounding and mediating effects of external factors.

Accordingly, for each of the 9 outcomes listed earlier we focused on evaluating both the total effect of preoperative

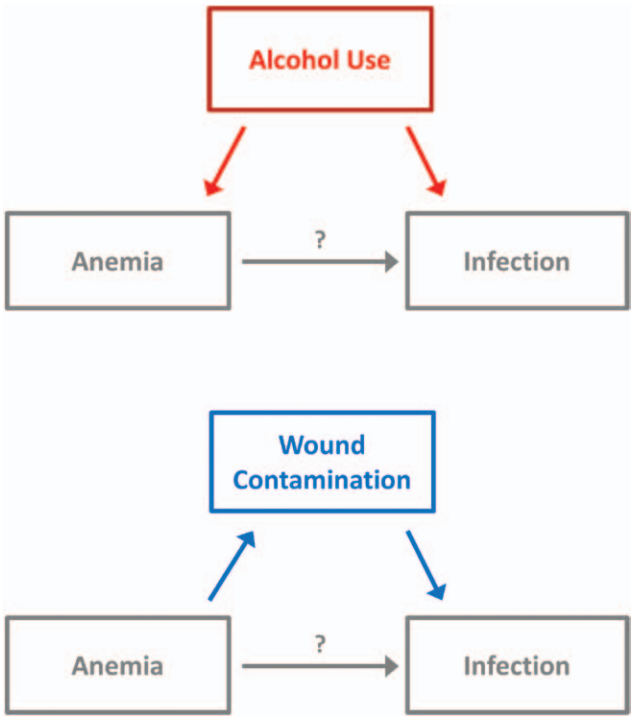

Figure 1. Examples of confounding (top panel) and mediating (bottom panel) effects of external factors in estimating the relationship between anemia and postoperative infection. Arrows are in the direction of assumed causality.

[a]World Health Organization. Iron deficiency anemia: assessment, prevention and control Available at: http://whqlibdoc.who.int/hq/2001/WHO_NHD_01.3.pdf. Accessed October 22, 2012.

anemia and the direct effect of preoperative anemia. For our total effect analysis on outcomes we decided, based on pathophysiology and clinical adjudication, not to adjust for the following possible mediating variables: intraoperative wound contamination, intraoperative RBC transfusion, duration of surgery, functional dependence before surgery, open wound preoperatively, and dyspnea. The direct effect analysis also adjusted for the mediator variables.

These 6 variables are plausible potential mediators as opposed to potential confounders. First, anything that occurs intraoperatively (e.g., intraoperative blood transfusion) can only affect the relationship between anemia and an outcome as a mediator because the intraoperative event occurs later in time than the anemia at baseline (thus, by definition it cannot be a confounder). Furthermore, although there is little plausible mechanism by which functional dependence before surgery may cause anemia, anemia has been shown to worsen physical performance.[29,30] Likewise, unless a preoperative open wound is so serious that it causes a massive loss of blood, it is quite unlikely that it can cause anemia; on the other hand, anemia has been associated with impaired wound healing.[31–33] Finally, anemia may cause dyspnea via reduced oxygen carrier capacity and impaired physical function, but dyspnea per se cannot cause anemia.

We adjusted for all the variables listed in Table 2 and primary procedure as potential confounders (primary procedure characterized using the United States Agency for Healthcare Research and Quality's Clinical Classifications Software [AHRQ-CCS], Rockville, MD[b]). Laboratory measures were excluded as potential confounders due to high frequencies of missing values.

Statistical Methods

Preliminary analyses using logistic regression and restricted cubic splines were performed to ascertain hematocrit ranges that exhibited maximal and minimal absolute risk of postoperative mortality.

The adjustment for potential confounders was performed via exact matching of anemic patients to nonanemic controls on AHRQ-CCS category, gender, race, and propensity score (propensity scores for being anemic [versus nonanemic] estimated using a multivariable logistic regression model including all potential confounders listed in Table 2 as predictors and rounded to the nearest percentage).

Assessment of balance on potential confounders before and after matching anemic patients to nonanemic controls was performed using absolute standardized differences (ASDs, defined as the difference in means, mean ranks, or proportions divided by a pooled estimate of the standard deviation). ASDs are used for matched studies because they do not depend on sample size like *P* values resulting from univariable tests of association. We regarded ASD >0.1 as indicative of some imbalance/potential confounding, and further adjusted for any such imbalanced covariables in our primary analyses (described in the ensuing sections).

In our primary analyses relating anemia to 30-day postoperative outcomes within the matched cohort, we estimated, for a given outcome, odds ratios representing the total effect of anemia. These odds ratios were estimated via respective multivariable logistic regression models. The Bonferroni correction for simultaneous inference on 9 outcomes was used to control the analysis-specific type I error rate at 5%. In our secondary analyses, the direct effect of anemia on each outcome was estimated by also adjusting for the purported mediator variables. R software version 2.12.1 for 64-bit Windows (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis.

RESULTS

There were 971,455 surgical cases available within the NSQIP database (Table 1). Of those, 272,554 cases (28.1%) did not meet our inclusion/exclusion criteria, and data were unavailable for another 124,041 patients. We therefore analyzed 574,860 patients. At baseline, 145,218 patients (25.3%) were anemic (65,456 male patients [28.5%] and 79,762 [23.1%] female patients).

Preliminary logistic regression analysis among these 574,860 patients revealed a maximum risk of mortality at preoperative hematocrit levels below 28% and minimum risk at hematocrit levels between 37% and 48%. However, anemic patients generally were of older age, lower body mass index, more severe ASA physical status, and were more likely to be of minority race, inpatients, diabetic, and hypertensive, among other baseline and intraoperative differences (Table 2, left panel). In all, 22 of 38 potential confounding variables had an ASD >0.1 before the matching.

Exact matching on propensity score, AHRQ-CCS procedure class, gender, and race resulted in nonanemic matched controls for 119,298 of 145,218 (82.2%) anemic patients. Thus, we included 238,596 patients for our final analysis. Before matching, the median (quartiles) propensity scores for the nonanemic and anemic groups, respectively, were 0.19 (0.13, 0.27) and 0.31 (0.20, 0.46); after matching, these statistics were 0.28 (0.19, 0.39) for both groups. Potential confounding variables were excellently balanced in the matched cohort (Table 2, right panel); the largest ASD of the 38 potential confounders was only 0.03.

The crude (unadjusted) mortality odds ratio was 4.69 (confidence interval, 4.01–5.49). Table 3 provides a summary of the estimated relationships between anemia and the 30-day outcomes of interest within the matched groups. The total effect of anemia was statistically significant for systemic, respiratory, urinary, thrombotic, and cardiovascular complications, as well as return to the operating room and mortality. Except for mortality, for which the total effect odds ratio (Bonferroni-adjusted 95% confidence interval) was 1.59 (1.42–1.78), total effect odds ratios for these outcomes varied between 1.20 and 1.30. On the other hand, the direct effects were all milder than the total effects with odds ratios of 1.24 (1.10–1.40) for mortality and odds ratios ranging between 0.95 and 1.13 for the complication outcomes. The odds ratios for systemic complications, respiratory complications, and cardiovascular complications were each no longer significant after accounting for the potential mediating effects; thus, our modeling indicated that anemia may affect these outcomes only through other channels, including the specified mediator variables, as opposed to having a direct effect.

[b]Healthcare Cost and Utilization Project (HCUP). January 2011. Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed October 22, 2012.

Table 2. Summary Statistics for Potential Confounding Variables, Before and After Propensity Matching and ASDs

	All patients			Matched patients		
	Nonanemic (*n* = 429,642)	Anemic (*n* = 145,218)	ASD	Nonanemic (*n* = 119,298)	Anemic (*n* = 119,298)	ASD
Female gender (versus male, %)	61.8	54.9	0.14	58.5	58.5	0.00
Race (%)						
Caucasian	74.6	68.4	0.23	71.9	71.9	0.00
African American	8.1	15.5		13.6	13.6	
Hispanic	7.0	6.8		6.2	6.2	
Asian	2.0	2.3		1.7	1.7	
Other	8.3	7.1		6.7	6.7	
Admitted directly from home (%)	99.2	95.4	0.23	98.0	97.9	0.00
Patient age (y, mean ± SD)	55.1 ± 15.7	60.6 ± 17.1	0.33	59.3 ± 15.9	59.5 ± 17.2	0.02
Height (in, mean ± SD)	66.0 ± 4.1	66.0 ± 4.2	0.00	65.9 ± 4.1	65.9 ± 4.1	0.00
BMI (kg/m^2, median [quartiles])	29 [25, 35]	27 [23, 32]	0.26	28 [24, 33]	28 [24, 33]	0.01
Current smoker (within 1 y, %)	20.4	17.7	0.07	18.8	17.9	0.02
Alcohol use[a] (%)	2.5	2.4	0.00	2.5	2.4	0.00
Diabetes mellitus (%)	12.5	22.7	0.27	18.5	19.4	0.02
Severe COPD (%)	3.8	6.2	0.11	5.6	5.6	0.00
CHF (in 30 d before surgery, %)	0.2	1.2	0.12	0.4	0.5	0.01
MI (in 6 mo before surgery, %)	0.2	0.7	0.09	0.4	0.4	0.01
Previous PCI (%)	4.2	7.4	0.14	6.8	6.7	0.00
Previous cardiac surgery (%)	4.1	9.4	0.21	8.2	7.8	0.02
Angina (in 1 mo before surgery, %)	0.4	0.9	0.06	0.7	0.8	0.01
Hypertension requiring medication (%)	44.7	57.5	0.26	53.5	55.0	0.03
Revascularization/amputation for PVD (%)	2.1	6.1	0.20	4.6	4.2	0.02
TIA (%)	2.4	4.0	0.09	3.5	3.7	0.01
CVA/stroke with neurologic deficit (%)	1.5	3.4	0.12	2.5	2.6	0.01
CVA/stroke with no neurologic deficit (%)	1.4	2.9	0.10	2.5	2.5	0.00
Do not resuscitate status (%)	0.2	0.9	0.10	0.4	0.4	0.00
Ventilator dependent (%)	0.0	0.1	0.04	0.0	0.0	0.01
Current pneumonia (%)	0.0	0.4	0.07	0.1	0.1	0.01
Ascites (%)	0.2	1.3	0.12	0.6	0.6	0.01
Esophageal varices (%)	0.0	0.2	0.05	0.1	0.1	0.00
Acute renal failure (%)	0.1	0.6	0.09	0.2	0.3	0.01
Preoperative dialysis (%)	0.8	3.7	0.20	1.8	2.1	0.02
Cancer[b] (%)	2.4	7.2	0.23	5.5	5.2	0.01
Impaired sensorium (%)	0.1	0.4	0.07	0.1	0.2	0.01
Coma >24 h (%)	0.0	0.0	0.01	0.0	0.0	0.00
Hemiplegia (%)	0.6	1.4	0.08	1.0	1.0	0.00
Paraplegia/quadriplegia (%)	0.4	0.9	0.06	0.6	0.6	0.00
Steroid use for chronic condition (%)	2.1	4.9	0.15	4.0	3.9	0.01
>10% loss body weight in last 6 mo (%)	1.3	5.1	0.22	3.3	2.9	0.03
Pregnancy (%)	0.1	0.3	0.06	0.1	0.2	0.01
Inpatient surgery (versus outpatient, %)	60.0	77.9	0.39	75.5	75.0	0.01
General anesthesia (versus other, %)	91.3	91.9	0.02	92.8	92.1	0.02
ASA classification (median [quartiles])	2 [2, 3]	3 [2, 3]	0.49	3 [2, 3]	3 [2, 3]	0.01

ASD is defined as the absolute value of the difference in means, mean rankings, or proportions divided by a pooled estimate of standard deviation. An ASD > 0.1 is indicative of slight imbalance between the 2 anemia groups and thus potential confounding of the relationship between anemia and a given outcome.

ASDs = absolute standardized difference; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack; CVA = cerebrovascular accident; ASA = American Society of Anesthesiologists.

[a]Alcohol use as defined by >2 drinks/d in 2 wk before admission.

[b]Disseminated cancer, history of radiotherapy/chemotherapy, or central nervous system tumor.

DISCUSSION

Preoperative anemia is common among surgical patients and is associated with considerable perioperative morbidity and mortality. In our study of 574,860 patients, approximately 25% of the patients were anemic. A total effect analysis, adjusting for confounding factors only, found an estimated 60% increase in the odds for postoperative 30-day mortality.

Our results differ from some of the previously published studies,[7,10,11] as we found a less pronounced effect of preoperative anemia on postoperative mortality. This can be explained 2-fold. First, available studies used different patient populations and second, we used the concept of confounding versus mediating factors, thus investigating the total effect of anemia in more detail.

With regard to different patient populations, the relationship between preoperative anemia and adverse outcomes might differ in elderly and sicker patients. For example, 1 retrospective study using an elderly Veterans Administration population from the National Surgical Quality Improvement Program database[11] found a 1.6% increase in the adjusted risk for 30-day mortality associated with every percentage point increase or decrease in

Table 3. Estimates of the Incidence of Nine 30-day Postoperative Outcomes for 238,596 Matched Anemic and Nonanemic Patients (n = 119,298 in each group), as well as Total Effect (Adjusting Only for Confounding Variables) and Direct Effect (Adjusting for Confounding and Mediator Variables) Odds Ratio Estimates Comparing Anemic with Nonanemic Patients on Each Outcome

Outcome	Incidence (%)		Direct effect odds ratio (95% CI[a]) (anemic versus nonanemic)	Total effect odds ratio (95% CI[a]) (anemic versus nonanemic)
	Nonanemic	Anemic		
Systemic complications	2.74	3.41	1.06 (1.00–1.13)	1.25 (1.18–1.33)[b]
Respiratory complications	2.35	3.02	1.06 (0.99–1.13)	1.29 (1.21–1.38)[b]
Wound infection	6.03	6.15	0.95 (0.90–0.99)[b]	1.02 (0.98–1.07)
Urinary complications	2.29	2.91	1.13 (1.06–1.21)[b]	1.28 (1.20–1.36)[b]
Central nervous system Complications	0.38	0.39	0.95 (0.80–1.13)	1.02 (0.87–1.21)
Thrombotic complications	0.87	1.08	1.12 (1.00–1.25)[b]	1.25 (1.12–1.39)[b]
Cardiovascular complications	0.51	0.66	1.10 (0.96–1.27)	1.30 (1.13–1.49)[b]
Return to operating room	4.36	5.19	1.10 (1.05–1.16)[b]	1.20 (1.14–1.26)[b]
Mortality	0.68	1.08	1.24 (1.10–1.40)[b]	1.59 (1.42–1.78)[b]

Analysis assumes the following potential mediating factors: intraoperative wound contamination, intraoperative red blood cell transfusion, duration of surgery, functional dependence before surgery, preoperative open wound, and dyspnea.

[a]Confidence intervals (CIs) adjusted using the Bonferroni correction for 9 outcomes to maintain an analysis-specific type I error rate of 0.05.

[b]Statistically significant odds ratios (after the Bonferroni correction).

the hematocrit value from the normal range. However, Wu et al[11] used the Veterans Administration National Surgical Quality Improvement Program database, whereas we used the American College of Surgeons NSQIP data set including broader types of surgeries, patient populations, and hospitals.[28] Thus, the data analysis by Wu et al includes a predominantly male and elderly patient population with more comorbidities. Furthermore, the time span of data collection (1997–2004) was different from ours (2005–2009). Improvements in surgical techniques and also in the anesthetic approach over the past 10 to 15 years might explain part of the difference.

In another single-center study from Canada, the authors showed that anemia is associated with a nearly 5-fold increase in postoperative mortality.[7] The unadjusted odds ratio comparing anemic NSQIP patients in our study was similar to that observed by the Canadian study; however, the estimated total effect odds ratio for 30-day postoperative mortality in our study was 1.59 (confidence interval, 1.42–1.78) compared with 2.36 observed by the Canadian study. A potential explanation for this observed difference might be that the Canadian study was a single-center study including major surgery and, probably, a sicker patient population.

The most recent and largest study to date in approximately 69,000 anemic patients also used the NSQIP data set and showed that even mild preoperative anemia is associated with 40% increased risk of 30-day mortality and 35% increased risk of 30-day morbidity.[10] The effect size in this study is close to our effect size, and it should be, as we used the same database. Nevertheless, the mortality odds ratio of 1.42 is less than our total effect odds ratio of 1.59. This most likely is the result of adjusting for different variables. For example, the authors adjusted for "perioperative transfusions" as a confounder, whereas we did not use transfusion as a confounder but rather as a mediator (and thus did not adjust for it) for our total effect analysis. This is an interesting example to point out that adjusting for different confounders might cause significant variation in effect size even when the same databases are being used.

The most important part of our study is the differentiation between the direct and total effect odds ratios for 30-day mortality and morbidity. For our main analysis, we estimated the total effect of anemia on mortality after adjusting for numerous known and documented comorbidities, but excluding from the adjustment those factors that might plausibly be considered as intermediate effects of anemia (mediators) with respect to postoperative 30-day morbidity and mortality. For this analysis, we made the assumption that any effects of these excluded variables on 30-day outcomes were at least partly the result of the patients' anemic status at baseline. The resulting odds ratio for mortality was 1.59. For our direct effect analyses, we further adjusted for the predefined mediator variables in addition to the confounders, with a reduced odds ratio for mortality of 1.24.

Indeed, we found evidence that anemia, largely through the mediating factors, was associated with significantly increased odds of the majority of outcomes under investigation. Presenting the 2 analyses demonstrates the ambiguity in understanding the results and improves on a single analysis that ignores the complex clinical relationships of anemia, covariables, and outcomes. The choice of confounders or mediators, however, is a clinical decision based on pathophysiologic mechanism, and there probably is no completely right or wrong answer. Dependent on the factors we choose, we might get effect sizes ranging from 20% to 60%. Thus, very careful consideration of variables used for adjustment is a prerequisite for every study using large databases. We recommend prespecifying mediating and confounding variables in the study protocol before analyzing data because this encourages investigators to make informed and clinically justifiable decisions, while at the same time supports accountability.

Like the most recent NSQIP study discussed earlier, we evaluated postoperative complications and showed that anemia (in conjunction with other variables considered to be part of the overall disease process of anemia) was associated with moderate increased risk of cardiac complications, central nervous system complications, respiratory complications, thrombotic events, wound infections, and return to the operating room. This is not surprising, as anemia in the surgical and nonsurgical setting seems to predict adverse outcomes.

In retrospective studies dealing with chronic exposures, it is important to distinguish between confounding and mediating variables. Adjusting for all available variables (confounding and mediating) potentially could "match away" the total effect of anemia occurring through mediating variables. As clinicians, we were interested in the total effect of anemia on outcomes via all possible pathways and therefore we propensity-matched anemic and nonanemic patients only on a priori–defined confounding variables.

Our study, and the 3 most recent studies, all used the World Health Organization definition for perioperative anemia. Indeed, the analyses of all 3 studies showed an increased risk of mortality with preoperative hematocrit levels deviating from 39%. In the study by Wu et al,[11] the odds ratio for 30-day death was close to 1 for the hematocrit range between 39% and 47%; similarly, our study shows maximum risk at preoperative hematocrit levels below 28% and minimum risk at hematocrit levels between 37% and 48% indicating that this range should be the goal to minimize risk. It is unknown whether preoperative anemia should be corrected before surgery. Furthermore, there are very few guidelines with regard to perioperative transfusion management. However, because of the well-known association between RBC transfusions and postoperative morbidity, clinicians typically use rather restrictive transfusion strategies. In fact, many studies show that perioperative hemoglobin levels of 5 to 7 are well tolerated by patients without major cardiac comorbidities with regard to cardiac performance, tissue oxygenation, systemic oxygen delivery, and overall postoperative morbidity.[34–37]

Despite the fact that the NSQIP database is a very large registry, it has some limitations. In our propensity matching, we adjusted for many confounders recorded in the NSQIP database. However, it is likely that some confounders were either not recorded or not known at the time of data collection. We, thus, cannot claim that anemia or the disease process marked by anemia has a causal relationship with outcome, only an association independent of those factors that were available to us for study. Also, approximately 10% of the patients did not have preoperative hematocrit values available and thus were excluded from the analysis. Although we have no reason to believe that patients with missing hematocrit values systematically differ from those included in the analysis, we cannot exclude the possibility of selection bias.

Our study is a retrospective analysis and thus does not allow any assumptions about causality between anemia and outcome. The association we identify between anemia and morbidly and mortality in no way proves that either outcome resulted from anemia per se, much less that intervening (i.e., transfusing RBCs) would improve outcomes. This is important, as it makes any conclusions about treatment options difficult. Thus, neither our study nor the 2 previous retrospective analyses indicate whether patients should be transfused perioperatively. Hematocrit correction before surgery might be preferable to intraoperative transfusion, especially as surgery induces an inflammatory response, which adversely affects the immune system. Allogeneic blood transfusion compromises the immune system as well and might cause a second hit to an already weakened immune system when performed in the intraoperative period.

In conclusion, this study demonstrates that preoperative anemia is independently associated with increased odds of postoperative 30-day mortality and morbidity.

DISCLOSURES

Name: Leif Saager, Dr med.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Leif Saager has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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ACKNOWLEDGMENTS

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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